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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,224	12/21/2001	Timothy E. Benson	00403.CN1	4497
26813	7590	04/19/2005	EXAMINER	
MUETING, RAASCH & GEBHARDT, P.A. P.O. BOX 581415 MINNEAPOLIS, MN 55458			STEADMAN, DAVID J	
			ART UNIT	PAPER NUMBER

1652

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/028,224

**Applicant(s)**

BENSON ET AL

**Examiner**

David J. Steadman

**Art Unit**

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2005.  
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 54-57, 59-61, 63, 65, 68-71 and 85 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 54-57, 59-61, 63, 65, 68-71 and 85 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.  
10) ☒ The drawing(s) filed on 11 June 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 2/15/05.  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.  
5) ☐ Notice of Informal Patent Application (PTO-152)  
6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Status of the Application***

**[1]** A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/15/2005 has been entered.

**[2]** Claims 54-57, 59-61, 63, 65, 68-71, and 85 are pending in the application.

**[3]** Applicants' amendment to the claims, filed 2/15/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

**[4]** Applicants' arguments filed on 2/15/2005 have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

**[5]** The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

### ***Claim Rejections - 35 USC § 112, Second Paragraph***

**[6]** The rejection of claim(s) 83, 86-87, 90, 93-100, 103, and 105-107 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' cancellation of the rejected claims.

**[7]** Claims 54-57, 59-61, 63, 65, 68-71, and 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear from claim 54 (claim(s) 55-57, 59-61, 63, 65, and 68-71 dependent therefrom) as to whether or not the method achieves crystallization of only human beta secretase of SEQ ID NO:1 or, alternatively, if the method achieves co-crystallization of the inhibitor bound to the active site of human beta secretase of SEQ ID NO:1. While it is acknowledged that the method requires preparation of human beta secretase of SEQ ID NO:1 "in the presence of an inhibitor," this is no indication that the inhibitor is present and is bound to the active site of the crystallized human beta secretase.

Similarly, it is unclear as to whether the inhibitor of the crystal of claim 85 is bound to the active site of the beta secretase of SEQ ID NO:1.

Solely for purposes of advancing prosecution, the examiner has interpreted claims 54 and 85 as meaning that the crystal of beta secretase is a co-crystal of the inhibitor bound to the active site of the beta secretase of SEQ ID NO:1. This interpretation is based on the disclosure of the specification, which teaches co-crystallization of beta-secretase and inhibitor, wherein the inhibitor is bound at the active site of beta-secretase (see p. 45, bottom, and p. 47, middle, of the specification).

If the examiner's interpretation of the claims is incorrect, applicants should so state and clarify the record.

While the examiner noted that "[o]ther than the provisional double patenting rejection, claim 85 appears to be in a condition for allowance" in the interview summary

mailed 2/9/2005, upon further consideration of claim 85, it is the examiner's position that the claim is unclear for the reasons stated above.

***Claim Rejections - 35 USC § 112, First Paragraph***

**[8]** The new matter rejection of claim(s) 86, 90, 95-96, 99-100, 103, and 105-107 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicants' cancellation of the rejected claims.

**[9]** The written description rejection of claims 54-76, 79-82, 84, 88, 91-93, 95, 97, 99, and 101-107 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicants' amendment to the claims.

**[10]** Claims 54-57, 59-61, 63, 65, and 68-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

In the amendment filed 2/15/2005, amended claim 54 (claim(s) 55-57, 59-61, 63, 65, and 68-71 dependent therefrom) recites the limitation "a solution comprising about 17% by weight to about 22% by weight PEG 3000." In the corresponding remarks, applicants assert "[t]he amendments to claim 54 are supported, for example, by the specification at page 45, line 22 to page 47, line 5; Figure 1; and originally filed claim 64" (p. 5, top). The examiner has carefully reviewed applicants' asserted support for amended claim 54. While the examiner can find support for a crystallization solution comprising "20% PEG 3000," "17-20% PEG 3000," or "17-22% PEG 3000," (p. 46), the examiner can find no support for the limitation of "a solution comprising about 17% by weight to about 22% by weight PEG 3000." As the examiner can find no support for the recited limitation, the claims fail to meet the written description requirement of 35 U.S.C. 112, first paragraph.

**[11]** The scope of enablement rejection of claims 54-57, 59-61, 63, 65, and 68-71 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and for the reasons stated below.

**RESPONSE TO ARGUMENT:** Applicants argue the rejection is overcome by amendment.

Applicants' argument is not found persuasive. The examiner maintains the position that the specification is enabling only for a method for crystallizing the human beta secretase of SEQ ID NO:1 bound to the human beta secretase inhibitor of Figure 1 by preparing purified human beta secretase of SEQ ID NO:1 in the presence of the inhibitor of Figure 1 to a final concentration of 18-40 mg/mL beta secretase protein and

2 mM inhibitor and crystallizing human beta secretase using the hanging drop method in a solution of 17-20% PEG 3000, 0.1 M sodium acetate, pH 4.5 at 20 degrees Celsius and optionally wherein the solution contains 10% glycerol or 10% ethylene glycol.

The examiner acknowledges that claim 54 has been amended to limit the sequence of the human beta-secretase and the conditions under which crystallization occurs. However, even as amended, the claims encompass a broad scope of crystallization conditions. The specification discloses working examples of crystallization conditions that resulted in successful co-crystallization of the protein of SEQ ID NO:1 and the inhibitor of Figure 1, resulting in diffraction-quality crystals. However, the specification fails to provide guidance regarding alteration of these conditions with an expectation of obtaining diffraction-quality crystals. Such guidance is necessary in view of the teachings of the prior art, which support a very high level of unpredictability regarding the alteration of crystallization conditions with an expectation of achieving diffraction-quality protein crystals. See teachings of Branden et al. (first cited in the Office action mailed 8/12/2003) and Drenth (cited by applicants in the IDS filed 2/12/2004). Also, Timasheff in the "Encyclopedia of Molecular Biology" (Creighton, T., John Wiley and Sons, Inc. New York, 1999) teaches, "[large, well-ordered crystals] are difficult to obtain. The crystallization of any given protein requires long painstaking work, including much trial and error in the choice of environmental conditions (pH, temperature) and crystallizing agents" (p. 586). In view of the broad scope of recited crystallization conditions, the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art (as evidenced by the cited teachings of Branden et

al., Drenth, and Timasheff), the lack of guidance and working examples in the specification, and the amount of trial-and-error experimentation required to test all possible combinations of crystallization conditions, it is the examiner's position that undue experimentation is required to make the full scope of the claimed invention.

***Double Patenting Rejection(s)***

**[12]** The provisional double patenting rejection of claims 54-71 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-18 of copending Application No. 10/027,277 and the provisional double patenting rejection of claims 54, 56, and 72-76 under 35 U.S.C. 101 as claiming the same invention as that of claims 4, 5, and 24-28 of copending Application No. 10/144,441 are withdrawn in view of the amendment to the claims.

**[13]** The provisional obviousness-type double patenting rejection of claims 54, 55, 57-71, 79-84, and 86-90 as being unpatentable over claims 1-3, 6-23, and 27-28 of copending Application No. 10/144,441, the provisional double patenting rejection of claims 54-69 as being unpatentable over claims 7-23 of copending Application No. 10/143,502, the provisional double patenting rejection of claims 54-67 as being unpatentable over claims 12-26 of copending Application No. 10/143,723, and the provisional double patenting rejection of claims 93-100 as being unpatentable over claim 1 of copending Application No. 10/027,277 are withdrawn in view of applicants' amendment to the claims.



**[14]** The provisional obviousness-type double patenting rejection of claim 85 as being unpatentable over claim 27 of copending Application No. 10/144,441 is maintained for the reasons of record.

**RESPONSE TO ARGUMENT:** Applicants argue the rejection has been rendered moot by amendment.

Applicants' argument is not found persuasive. The examiner maintains that claim 85 is not patentably distinct from claim 27 of the '441 application, particularly in view of the specifically disclosed embodiment in the specification of the '441 application that supports claim 85 of the instant application.

### ***Conclusion***

**[15]** Status of the claims:

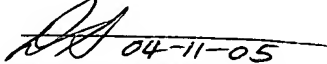
- Claims 54-57, 59-61, 63, 65, 68-71, and 85 are pending.
- Claims 54-57, 59-61, 63, 65, 68-71, and 85 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday and on alternate Fridays from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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04-11-05  
**DAVID J. STEADMAN, PH.D.**  
**PRIMARY EXAMINER**